REMARKS/ARGUMENTS

Status of the Claims

Claims 1-33 and 52-58 were rejected. Claims 34-51 have been withdrawn from consideration as being drawn to non-elected inventions. To expedite prosecution, claims 1-8, 11, 18, 26-33, and 52-56 have been canceled without prejudice or disclaimer. Applicants reserve the right to pursue these claims in a continuation or divisional application or to take other such appropriate action to seek protection of this canceled subject matter.

Claims 9, 12, 17, and 20 have been amended to clarify the invention. In particular, formerly dependent claims 9 and 12 have been re-written as independent claims such that they now recite the limitations of original claims 1 and 9 or 1 and 12, respectively. Claim 17 has been amended to incorporate the limitations of original claim 18. Claim 20 has been amended to depend from claim 19. Accordingly, claim 18 has been canceled. No new matter has been added by way of the claim amendments.

Claims 9, 10, 12-17, 19-25, 57, and 58 are now pending in the present application. Reexamination and reconsideration of the claims are respectfully requested in view of the claim amendments and the following remarks. The Examiner's rejections in the Office Action are addressed below in the order set forth therein.

The Objections to the Claims Should Be Withdrawn

Claims 4, 12, 19, and 27 were objected to for minor informalities. The objections to claims 4 and 27 have been obviated by the cancellation of these claims. Claims 12 and 19 were objected to for minor typographical errors. Applicants appreciate the Examiner bringing these errors to their attention and have amended claims 12 and 19 accordingly. In light of the cancellation of claims 4 and 27 and the amendment of claims 12 and 19, Applicants respectfully request that the objections to the claims be withdrawn.

Claims 53-55 were objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. As indicated above, claims 53-55 have been canceled to further prosecution. Therefore, the objection to claims 53-55 has been obviated and should be withdrawn.

The Rejection of Claim 29 Under 35 U.S.C. § 112, Second Paragraph, Should be Withdrawn

Claim 29 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. To expedite prosecution, claim 29 has been canceled. Accordingly, the rejection of claim 29 under 35 U.S.C. § 112, second paragraph, has been obviated and should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 102 Should be Withdrawn

Claims 1-5, 8, 11, 26, 27, 32, and 53-55 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,383,754 (hereinafter "the '754 patent"). This rejection is respectfully traversed as to the pending claims.

The present claims are directed to a method for preparing a DNA fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA comprising preparing a nucleic acid that comprises a nucleotide sequence of the 5' end of an mRNA, attaching at least one linker to the nucleic acid, cleaving the nucleic acid with a restriction enzyme having its recognition site within the linker and its cleavage site within the nucleic acid corresponding to the 5' end of the mRNA, and collecting a resulting DNA fragment corresponding to the 5' end of the mRNA molecule. The independent claims have been amended to more clearly define the invention and now recite that the 5' end region includes the most 5' end of the mRNA. The Examiner maintains that the '754 patent teaches all of the steps recited in the claims. Applicants respectfully disagree with this conclusion.

The method disclosed in the '754 patent requires internal cleavage of a cDNA for analysis and, therefore, does not allow for analysis of the nucleotide sequence of the most 5' end. In Illustration 4 cited by the Examiner, a Type IIS or Type II enzyme (i.e., enzymes that cleave outside of their recognition sequences) is used to cleave the cDNA in the first step. This cleavage makes use of recognition sites within the cDNA, and a Type IIS or Type II enzyme is used to create a 4 nucleotide overhang at the 5' end of the digestion product. Since these enzymes cleave outside of their recognition sequence, the digestion products can have up to 256

(i.e., 4^4) different sequences within the 4 nucleotide overhang. The '754 patent uses offset adaptors to read the 256 different overhang sequences in a hybridization and ligation reaction.

The method of the '754 patent is similar to the categorization of DNA fragments by a method generally known as "molecular indexing" which uses adaptor molecules hybridizing to the ambiguous overhangs generated by cleaving nucleic acid molecules with a Type IIS restriction endonuclease. Therefore, the method of the '754 patent neither isolates sequence information from the most 5' end having about 5-50 basepairs of the original mRNA/RNA nor does the method of the cited reference provide a means to sequence this information. Moreover, the '754 patent does not teach anything about specific means to enrich 5' ends of mRNA by making use of a cap structure that marks the 5' end of mRNA in biological samples. The method of the cited reference is likely to divide the cDNA into various fragments that are unrelated to the most 5' end of the original mRNA.

Although Applicants maintain that the present claims are not anticipated by the '754 patent for the reasons set forth above, this rejection has been obviated by the cancellation of claims 1-5, 8, 11, 26, 27, 32, and 53-55 and should be withdrawn. Applicants further note that pending claims 9, 10, 12-17, 19-25, 57, and 58 were not rejected as being anticipated by the '754 patent.

Claims 1-8, 11, 17, 19-21, 23-33, and 52-56 were further rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Application Publication No. 2003/0113737 (hereinafter "the '737 publication"). This rejection is respectfully traversed as to the pending claims.

The '737 publication discloses a method similar to the process of "molecular indexing," although the approach of the method of the cited reference targets the isolation of single-stranded tags for analysis. Such single-stranded tags are isolated by means of one or two restriction endonucleases, one of which preferably nicks double-stranded DNA, wherein the nicked DNA strand will yield the single-stranded tag. The location and length of the singled-stranded tag is determined by the position of the recognition site(s) and the type of restriction endonucleases used.

Moreover, the methods of the '737 publication require single-stranded DNA for further manipulation and analysis. These sites can be randomly distributed within the DNA, which implies that the site will likely be away from the sequence corresponding to the transcription start site. In addition, the location of the single-stranded tag is determined by the position of the recognition site and the type of restriction endonuclease used, whereas in the method of the present invention the 3' end of the tags is determined distance between the recognition site of the endonuclease and the site where the enzyme cleaves the double-stranded DNA. In contrast to the presently claimed methods, the '737 publication does not teach how to specifically isolate tags starting from the most 5' nucleotide of the mRNA.

Although Applicants maintain that the present claims are not anticipated by the '737 publication for the reasons set forth above, this rejection has been obviated by the cancellation of claims 1-8, 11, 17, 19-21, 23-33, and 52-56 and should be withdrawn. Applicant notes that claims 9, 10, and 12-16, and 22 were not rejected as being anticipated by the '737 publication. Furthermore, as discussed above, claim 17 has been amended to incorporate the limitations of original claim 18. Original claim 18 was not subject to the present rejection, and, therefore, amended claim 17 is also not anticipated by the '737 publication. As claims 19-21 and 23-25 depend from amended claim 17, Applicants respectfully maintain that the rejection of claims 19-21 and 23-25 has been obviated by the amendment of claim 17.

The Examiner has maintained the rejection of claims 1-5, 8, 11, 26-28, 30, 32, 33, and 53-55 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,695,937 (hereinafter "the '937 patent"). Although Applicants maintain that the present claims are not anticipated by the '937 patent for the reasons set forth below, this rejection has been obviated by the cancellation of claims 1-5, 8, 11, 26-28, 30, 32, 33, and 53-55 and should be withdrawn.

Claims 1-5, 8, 11, 26-32, and 53-55 were again rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Application Publication No. 2004/0002104 (hereinafter "the '104 publication"). This rejection has been obviated by the cancellation of claims 1-5, 8, 11, 26-32, and 53-55 and should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 6, 31, and 52 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the '937 patent in further view of Maruyama *et al.* (1994) *Gene* 138:171-174. This rejection has been obviated by the cancellation of claims 6, 31, and 55 and should be withdrawn.

Claims 9, 10, 12, 14-16, and 58 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the '937 patent in further view of Carninci *et al.* (1996) *Genomics* 37:327-336. This rejection is respectfully traversed.

The '937 patent discloses a method for Serial Analysis of Gene Expression (SAGE) that permits numerous transcripts to be analyzed in order to determine the overall gene expression pattern in various cell types. As discussed in paragraphs [0005] through [0010] of the present application, the 3' ends of mRNA molecules, rather than the 5' ends recited in the claims, are collected with high prevalence via the SAGE method disclosed in the '937 patent. Further evidence in support of this statement is provided in Velculescu *et al.* (1995) *Science* 270: 484-487. See, particularly, pages 484, right-hand column; page 486, left-hand column; and Table 2. A copy of this reference was previously submitted for the Examiner's consideration. In contrast to the techniques disclosed in the '937 patent, the present method claims recite the collection of the DNA fragments corresponding to the most 5' end of mRNAs. The collection of such 5' end fragments is particularly advantageous for such applications as promoter mapping and analysis, which simply cannot be accomplished using molecules corresponding to the 3' ends of mRNAs. Applicants further note that the method disclosed in the cited reference cannot be used to obtain the most 5' end of an RNA having a cap structure or any cDNA derived therefrom.

The '937 patent only teaches the *possibility* of the isolation of sequences in relation to the most 5' recognition site of an endonuclease, which is unlikely to include the most 5' sequence of an mRNA or any cDNA derived therefrom. The cited reference does not teach a specific method for obtaining the most 5' sequence from a pool of digested nucleic acid fragments. As discussed herein above, the 5' sequences obtained by the method of the '937 patent are not equivalent to the most 5' end of mRNAs that are obtained via the claimed methods. The "5' ends" that are

obtained according to the method of the '937 patent may be 100 basepairs or more from the transcription start site. Applicants reiterate the importance of obtaining the most 5' end of an mRNA, as this sequence contains transcription start site and related promoter regions. Such sequences permit analysis of transcription start site and promoter identification in genomic sequences.

Applicants further note that the method disclosed in the '937 patent requires two digestion steps utilizing two endonucleases. The first endonuclease cleaves the cDNA at a defined position in the cDNA, thereby producing the defined sequence tags. That is, the first digestion marks the location of the DNA fragment that is isolated in a second digestion step. The first digestion step makes use of an internal recognition sit within the cDNA, and the location of such recognition site depends on each mRNA molecule. Since the method of the cited reference requires an internal recognition site, it cannot isolate the most 5' nucleotides of an mRNA or cDNA molecule. In contrast to the method of the '937 patent, the instant method uses only one endonuclease digestion step, and the recognition site for the endonuclease is introduced by a linker placed adjacent to the 5' end of an mRNA or a cDNA derived therefrom. Indeed, the strategy disclosed in the '937 patent is based on the above cDNA cleavage, which would cleave elsewhere *inside* the transcripts. Therefore, the "5' end" of a DNA fragment obtained by the method of the '937 patent does not correspond to the mRNA/RNA transcription start site

The Carninci *et al.* reference is drawn a method for constructing high-content full-length cDNA libraries based on chemical introduction of a biotin group into the cap structure of a eukaryotic mRNA molecule. This reference does not teach or suggest utilizing any 5' cap structure in a method for preparing DNA *fragments* corresponding to a nucleotide sequence of a 5' end region of an mRNA, as recited in all of the rejected claims. The Examiner maintains that it would have been obvious to one of skill in the art to combine the disclosures of the '937 patent and the Carninci *et al.* reference to produce the methods of claims 9, 10, 12, 14-16, and 58. Applicants respectfully disagree with the Examiner's conclusions.

Establishing a *prima facie* case of obviousness requires assessment of the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), which

provides the framework for applying the statutory language of § 103. Under the "Graham Factors," the Examiner is required to:

1. Determine the scope and content of the prior art;
2. Ascertain the differences between the prior art and the claims at issue;
3. Resolve the level of ordinary skill in the pertinent art; and
4. Consider any relevant secondary considerations.

Although Applicants do not concede that a *prima facie* case of obviousness has been established for claims 9, 10, 12, 14-16, and 58, secondary considerations of the advantageous properties of the claimed methods (e.g., the collection of molecules corresponding to 5' mRNA ends by the practice of the present methods versus the high prevalence of 3' mRNA ends collected via the SAGE technique disclosed in the '937 patent, provide additional support for the nonobviousness of the pending claims (see, for example, paragraphs [0005] through [0010] of the present application). See *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) and *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). As discussed above, the collection of fragments corresponding to the 5' end of an mRNA molecule rather than the 3' end permits, for example, promoter mapping and analysis. The method of the '937 patent results primarily in the collection of 3' ends of mRNA molecules and does not any provide information regarding the 5' end of transcripts or allow for promoter analysis. Applicants respectfully remind the Examiner that the secondary consideration of superior and advantageous results obtained with an invention provides objective indicia of nonobviousness. See, for example, *In re Mayne*, 104F.3d 1339, 1342, 41USPQ2d 1451, 1454 (Fed. Cir. 1997) and *In re Woodruff*, 919F.2d 1575, 1578, 16 USPQ2d 1934,1936-37 (Fed. Cir. 1990). Such "secondary considerations" as those noted above further support the conclusion that the rejected claims are not obvious.

Applicants further note that combining the method of the '937 patent with the oligo capping and cap trapper methods of the Carninci *et al.* reference leads to the isolation of DNA fragments that are clearly distinct from the most 5' end obtained by the present method, both in their sequence and their location within the mRNA or cDNA derived therefrom. Thus, it is not obvious to combine the cited references.

Moreover, although the U.S. Supreme Court declined to permit a "rigid" application of the teaching-suggestion-motivation to combine (TSM) test to obviousness determinations, the Court did hold that the presence or absence of a teaching, suggestion, or motivation to combine the cited references provides a "helpful insight" regarding the obviousness of an invention. *KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1389 (U.S. 2007). The Supreme Court went on to acknowledge the importance in making obvious determinations of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does." *Takeda Chemical Industries, Ltd. V. Alphapharm Pty., Ltd.*, 83 USPQ2d 1169, 1174 (Fed. Cir. 2007; citing *KSR Int'l Co. v. Teleflex, Inc.*).

In the instant case, the Examiner has merely pieced together the claimed invention by citing two unrelated references, namely the first drawn to a method for analysis of transcripts in order to determine the overall pattern of gene expression (i.e., the '937 patent) and the second directed to full-length cDNA cloning (i.e., Carninci *et al.*). Given the lack of evidence of a reason to combine the references, it appears that the Examiner has engaged in impermissible "hindsight reconstruction" in formulating the present rejection. See *In re Fine*, 5 USPQ2d 1071, 1075 (Fed. Cir. 1988) (holding that "[o]ne cannot use hindsight reconstruction to pick and choose among disclosures in the prior art to deprecate the claimed invention") and *Graham v. John Deere Co.*, *supra* (stating the importance of guarding against "slipping into hindsight and…resisting [the] temptation to read into the prior art the teachings of the invention in issue"). Therefore, in establishing obviousness, it is improper "to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). Accordingly, the lack of a *reason* to combine the cited references to arrive at the claimed methods provides additional evidence that claims 9, 10, 12, 14-16, and 58 are not obvious.

In view of the above remarks, the secondary considerations of nonobviousness, particularly the superior and advantageous results obtained by the practice of the claimed methods (e.g., the collection of DNA fragments corresponding to the 5' end of an mRNA), and the lack of a reason to combine the cited references, Applicants respectfully request that the rejection of claims 9, 10, 12, 14-16, and 58 under 35 U.S.C. § 103(a) be withdrawn.

Claims 13 and 57 were again rejected under 35 U.S.C. § 103(a) as being unpatentable over the '937 patent in further view of Carninci *et al.* (1996) *Genomics* 37:327-336, Edery *et al.* (1995) *Mol. Cell. Biol.* 15(6):3363-3371, and Das *et al.* (2001) *Physiol. Genomics* 6:57-80. This rejection is respectfully traversed.

The teachings of the '937 patent and the Carninci *et al.* reference are described above. The Edery *et al.* reference discloses a method for isolating full-length cDNAs based on an mRNA cap retention procedure. The Das *et al.* reference is simply a review article that analyzes and compares a variety of techniques for isolating full-length cDNAs. Neither Edery *et al.* nor Das *et al.*, however, teach or suggest the preparation and collection of DNA fragments corresponding to the most 5' end of mRNAs. The Examiner concludes that one of skill in the art would have motivated to combine the cited references to arrive at the methods of claims 13 and 57. Applicants respectfully disagree with the Examiner's assertions.

Applicants reiterate that secondary considerations such as superior and advantageous properties support the nonobviousness of claims 13 and 57. In particular, the methods of the rejected claims result in the collection of DNA fragments corresponding to the 5' ends of mRNAs, thereby permitting, for example, promoter mapping and analysis that cannot be achieved with samples comprising the 3' ends of transcripts in high prevalence, such as those obtained by the methods of the '937 patent. Moreover, Applicants respectfully submit that the Examiner has merely "pieced together" four unrelated references to allegedly produce the claimed methods without providing a sufficient "reason" that one of skill in the art would have been motivated to combine these references. Such "hindsight reconstruction" is impermissible.

In view of the above remarks, the secondary considerations of nonobviousness, specifically the superior and advantageous results obtained by the practice of the claimed methods (e.g., collection of DNA fragments corresponding to the 5' end of an mRNA molecule), and the lack of a reason to combine the four cited references, Applicants respectfully request that the rejection of claims 13 and 57 under 35 U.S.C. § 103(a) be withdrawn.

Claim 18 was rejected under 35 U.S.C. § 103(a) as being unpatentable over the '737 publication in view of Shibata *et al.* (2001) *Biotechniques* 30(6):1250-1254. As discussed above, the limitations of original claim 18 have been incorporated into claim 17. Therefore, this rejection will be addressed insofar as it may apply to present claim 17.

The '737 publication is drawn to a method for obtaining reproducible representations of expressed mRNA molecules by utilizing short polynucleotide tags comprising nucleotide sequence information. The Examiner has acknowledged that the '737 publication "does not teach that the first strand cDNA is ligated to a double-stranded linker, which is then used to prime second strand cDNA synthesis, as required by claim [17]." See page 22, Office Action mailed March 4, 2008. The Shibata *et al.* reference discloses a method for construction of a mouse full-length cDNA encyclopedia. The Examiner maintains that it would have been *prima facie* obvious to one of skill in the art to combine the disclosures of the '737 publication and the Shibata *et al.* reference to arrive at the method of claim present claim 17 (i.e., formerly claim 18). Applicants respectfully disagree with the Examiner's conclusions.

Applicants submit that the Examiner has failed to provide a sufficient "reason" that one of skill in the art would have been motivated to combine these references to produce the claimed method, as required by the present case law. Specifically, in contrast to present claim 17, which expressly recites "collecting a resulting DNA fragment corresponding to the 5' end of an mRNA" (emphasis added), the Shibata *et al.* reference actually *teaches away* from producing and collecting DNA fragments. As acknowledged by the Examiner, the authors of the cited reference indicate that their method is "especially suitable for synthesizing and cloning full-length cDNA molecules" (emphasis added). See page 23, Office Action mailed March 4, 2008 and page 1253 of the Shibata *et al.* reference. In the instant case, the Examiner has merely pieced together the claimed invention by citing references that allegedly teach elements of the claims. Accordingly, the Examiner appears to have "arrived" at the claimed method by citing references that teach claim elements without providing a sufficient reason to combine these references. Given the lack of evidence of a reason to combine the references and the observation that the Shibata *et al.* reference actually teaches away from the method of claim 17, it appears that the Examiner has engaged in impermissible "hindsight reconstruction."

Therefore, in light of the above remarks, Applicants respectfully request that the obviousness rejection of present claim 17 (i.e., formerly claim 18) under 35 U.S.C. § 103(a) be withdrawn.

Claim 22 was also rejected under 35 U.S.C. § 103(a) as being unpatentable over the '737 publication in view of U.S. Patent No. 5,484,701 (hereinafter "the '701 patent). Again, claim 17 has been amended to incorporate the limitations of claim 18. Claim 22 ultimately depends from and therefore recites all of the elements of present claim 17. This rejection will be addressed insofar as it may apply to dependent claim 22 in view of the amendment of independent claim 17.

The teachings of the '737 publication are described above. The '701 patent is drawn to a method for isolating primer extension products and generating them in a form appropriate for electrophoresis by utilizing the biotin-avidin/streptavidin system or a digoxigenin-digoxigenin antibody capture system. In particular, the '701 patent describes a method for enrichment or purification of primer extension products by making use of a biotinylated primer, enriching the biotinylated reaction product on a solid support having an immobilized biotin-binding protein attached to it, and removing the biotinylated reaction product from the solid support by formamide treatment. Enriched reaction products are preferably analyzed by gel electrophoresis. The use of a biotin group in the present invention is unrelated to the method of the '701 patent, specifically because the '701 patent neither teaches the purification product obtained from a primer extension product nor does the reference teach the release of the reaction product by the use of PCR, as recited in the present claims. The Examiner asserts that the skilled artisan would have been motivated to combine the teachings of the '737 publication and the '701 patent to arrive at the method of claim 22. Applicants respectfully disagree with the Examiner's conclusions.

As noted above, claim 17 has been amended to incorporate the elements of claim 18, and claim 18 has therefore been canceled. In the above obviousness rejection of original claim 18 (i.e., present claim 17), the Examiner herself has acknowledged that the '737 publication "does

not teach [the recited element of claim 17] that the first strand cDNA is ligated to a double-stranded linker, which is then used to prime second strand cDNA synthesis." See page 22, Office Action mailed March 4, 2008. This deficiency is not cured by the teachings of the '701 patent.

A *prima facie* case of obviousness under 35 U.S.C. § 103(a) requires that the combination of references places the claimed subject matter in the public domain prior to Applicants' date of invention. See *In re Zenitz*, 333 F.2d 924, 142 USPQ 158 (C.C.P.A. 1964). Thus, establishing a *prima facie* case of obviousness requires that the cited references can be combined such that each and every element of the claimed invention is taught, explicitly or implicitly, by the references and that a reasonable expectation of success exists in such a combination. In the instant case, the cited references do not disclose, either explicitly or implicitly, the recited claim element of ligation of the first strand cDNA to a double-stranded linker, which is then used to prime second strand cDNA synthesis. Thus, the disclosures of the cited references simply cannot be combined to arrive at the claimed method. Furthermore, although in the present case the references simply cannot be combined to produce the claimed invention, the Examiner has also merely provided broad conclusory statements and has failed to identify a sufficient reason that one of skill in the art would have been motivated to combine the cited references and would have concluded that the method of claim 22 is obvious in view of this combination.

Accordingly, in view of the above remarks, Applicants respectfully request that the obviousness rejection of claim 22 be withdrawn.

CONCLUSION

The Examiner is respectfully requested to withdraw the rejections of the claims. In view of the above remarks and claim amendments, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

/michelle l. cunningham/
Michelle L. Cunningham
Registration No. 51,072

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

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